

FUNCTIONAL CONSEQUENCES OF BASAL GANGLIA PATHOLOGIES

Ph.D. dissertation

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- II. Antal A, **Beniczky S**, Kincses T, Jakab K, Benedek G, Vécsei L: Perceptual categorisation is impaired in Huntington's disease: an electrophysiological study. *Dementia and Geriatric Cognitive Disorders*, 2003; 16(4): 187-92.
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- II. **Beniczky S, Antal A., Benedek G., Vécsei L.:** Electrophysiological changes in diseases affecting the basal ganglia. *Hippocrates* (2000), 6: 358-360.(Hungarian).

LIST OF ABBREVIATIONS

CCT. Central conduction time.

CM/pf. Centromedian and parafascicular nuclei of the thalamus.

CNS. Central nervous system.

CTX. Cerebral cortex.

DLPFC. Dorsolateral prefrontal cortex.

DYN. Dynorphin.

ENK. Enkephalin.

ERPs. Event-related potentials.

GABA. γ -aminobutyric acid.

GLU. Glutamine.

GPe. Globus pallidus, external part.

GPi. Globus pallidus, internal part.

HD. Huntington's disease.

HDC. Asymptomatic carriers of the CAG repeat extension..

MSN. Medium spiny neurons.

PCL. Probabilistic classification learning.

PD. Parkinson's disease.

SEPs. Somatosensory evoked potentials.

SMA. Supplementary motor area.

SNc. Substantia nigra, pars compacta.

SNr. Substantia nigra, pars reticulata.

SP. Substance P.

STN. Subthalamic nucleus.

TH. Thalamus.

VA. Ventral-anterior.

VL. Ventral-lateral.

WCST. Wisconsin Card Sorting Test.

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I.

SUMMARY

The basal ganglia are large subcortical nuclear masses that are interconnected with all cortical areas, and that receive updating (via thalamus) from most of the pathways leaving and targeting the cortex. This strategic position enables the basal ganglia to play a leading role in the synchronization of a wide range of central nervous system (CNS) functions. In an attempt to further elucidate the importance of these structures, we investigated the consequences of basal ganglia dysfunction (especially those of the striatum) at three levels of integration: primary perception, perceptual categorization/decision process and cognitive functions.

We addressed the changes in primary perception and cortical excitability using somatosensory evoked potentials (SEPs). Perceptual categorization and decision-making was assessed by means of event-related potentials (ERPs) based on a visual categorization task. Cognitive impairment was investigated using a battery of tests with special emphasis on attentional set-shifting and habit-learning.

As models for basal ganglia dysfunction (and specifically striatal damage), we included Huntington's disease (HD) patients, their symptom-free relatives at risk (carrying the genetic mutation, a CAG trinucleotide expansion) and a patient with focal vascular lesions of the right striatum.

SEPs and ERPs revealed diminished cortical amplitudes in HD and in focal lesions of the striatum, which indicates that cortical excitability is decreased when striatum is damaged. The amplitude reduction of the median nerve SEPs in HD was proportional to the extent of the genetic mutation i.e. the length of the trinucleotide repeat. It is the first time one could establish a correlation between the magnitude of a trinucleotide expansion and the extent of the neurophysiological consequence. Tibial nerve SEPs proved to be a sensitive method for detection of early pathophysiological changes in HD, in our study being the only neurophysiological alteration in asymptomatic carriers of the mutation. Focal lesions of the striatum differentially affected the cortical components of the median nerve SEPs, with more severe impairment of the frontal than the parietal components.

Perceptual categorization/decision process showed a specific pattern of alteration in HD, according to the ERPs. The category-specificity of a negative wave starting at 150 ms post-stimulus was impaired at the temporal recording sites. These data further emphasize the

importance of striato-temporal circuits in the visual categorization/decision process. Since this pattern of alteration is different from both patients with Parkinson's disease and focal vascular lesions, our results demonstrate that different basal ganglia pathologies have distinct neurophysiological consequences.

Focal lesions of the striatum caused a significant impairment in habit learning. This is in consistence with data from HD patients, concerning the involvement of the striatum in this cognitive function. We also proved that attentional set-shifting (executive dysfunction) is independent from habit learning problems.

Taken together, our data suggest that striatum plays a crucial role in the organisation of such distinct CNS functions as primary perception, perceptual categorisation/decision and habit learning. Thus clinical consequences of striatal damage must be thought off as a summation of these multilevel malfunctions.

II.

INTRODUCTION

1. ANATOMY OF THE BASAL GANGLIA

There is still a debate on the number of structures that are part of the basal ganglia. The main components are five nuclei: the caudate nucleus (with the adjacent nucleus accumbens), putamen, the subthalamic nucleus, substantia nigra and the globus pallidus. However, based on the tight functional connections, some authors refer to the central complex of the thalamus, amygdala and hippocampus as parts of the basal ganglia (Herrero et al. 2002, Obeso et al. 2002, Ring and Serra-Mestres 2002, Yelnik 2002).

The caudate nucleus (consisting of head, body and tail) and the putamen form together the striatum. The putamen and globus pallidus are described as the lentiform nucleus. These structures are situated deep in the hemispheres, lateral to the thalamus and lateral ventricles. Globus pallidus (forming the medial part of the lentiform nucleus) is subdivided into an external (GPe) and an internal (GPi) part. Substantia nigra, situated in the rostral part of the midbrain, next to the cerebral peduncles, comprises two major subdivisions: the pars compacta (SNc) that is rich in dopaminergic cells and the pars reticulata (SNr). The subthalamic nucleus (STN) has the shape of a biconvex lens and is situated between the thalamus and the substantia nigra.

Recently an additional term, “ventral striatum” has been introduced to describe the parts of the basal ganglia closest to the limbic system and that are involved in cognitive and behavioral functions. These are the nucleus accumbens (located on the ventromedial side of the head of the caudate nucleus) and the ventral part of the caudate/putamen (Alheid et al. 1990). Within the ventral striatum one can differentiate the core and the shell. The latter has a rich dopaminergic innervation arising from the ventral tegmental area and dense innervation from the basolateral complex of the amygdala (Everitt 1999).

Striatal neurons are mainly (96%) inhibitory GABA-ergic neurons, whose dendrites are covered with dendritic spine (“medium spiny neurons, MSN”). Their axon gives dense local collateral arborization to other medium spiny neurons. These cells express enkephalin or substance P and dynorphin. The remaining 4% are interneurons: large, aspiny cholinergic neurons that are involved in learning reward behavior, and small GABA-ergic interneurons that contribute to the surrounding inhibition. In contrast, the pallidal and nigral neurons have

The major input structure of the basal ganglia is the striatum (figure 1). Most of the information comes from the cortex. The ventral striatum receives a prominent projection from the amygdala. The striatum is also a major target of the dopaminergic neurons from SNc.

The major output structures of the basal ganglia are the GPi and the SNr. Via the anterior and lateral nuclei of the thalamus the pallidal output is then transferred to the frontal cortex, supplementary motor area (SMA), while the nigral output is directed mainly to the dorsolateral prefrontal cortex. Globus pallidus and STN receive dopaminergic inputs too, but to a lesser degree than the striatum (figure 1).

The volume of the striatum is 20 times larger than that of the GPi and SNr (Yelnik 2002). This dramatic decrease suggests an important convergence of information between the input and the output structures.

There are (at least) two different ways, the input and output structures of the basal ganglia connect (figure 2). The direct pathway (striatum-GPi/SNr) has an excitatory effect on the thalamic neurons and, on turn, to the cortex (Albin et al. 1989). The indirect pathway (striatum-GPe-STN-GPi/SNr) has an inhibitory final outcome. Striatal neurons that express substance P and endorphyn are thought to be part of the direct pathway, and to receive excitatory dopaminergic inputs (D1 receptors). In contrary, MSN that take part in the formation of the indirect pathway are expressing enkephalin and receive inhibitory dopaminergic inputs (D2 receptors). This model can explain why the loss of nigrostriatal neurons in Parkinson's disease (PD) leads to a pauperization of movement pattern (decreased activity in the excitatory-direct pathway, and decreased activity in the inhibitory-indirect pathways).

Recently, a "hyperdirect" cortico-subthalamo-pallidal pathway was described, that bypasses the striatum (Nambu et al. 2002). It was hypothesized that at the beginning of a movement initiation, this pathway inhibits large areas of the thalamus and cortex that are related to both the selected motor program and other competing programs. Then another signal, disinhibits the selected program through the direct pathway. Finally, impulses through the (inhibitory) indirect pathway terminates the action.

Initially only two parallel subcortical loops were suggested: a motor loop passing through the putamen and an association ("complex") loop passing through the caudate.

Subsequently five parallel circuits were identified: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and limbic / anterior cingulate circuits (Alexander et al. 1986). However the complexity of the connections is much higher.

In addition to these “external” loops, there are several “internal” circuits, interconnecting subcortical nuclei. Most of these are thalamo-basal ganglia-thalamic “closed” loops: centromedian / parafascicular thalamic nuclei (CM/pf)-striatum-GPi-CM/pf (positive feedback loop), CM/pf-striatum-STN-GPi-CM/pf (negative loop) (Obeso et al. 2002).

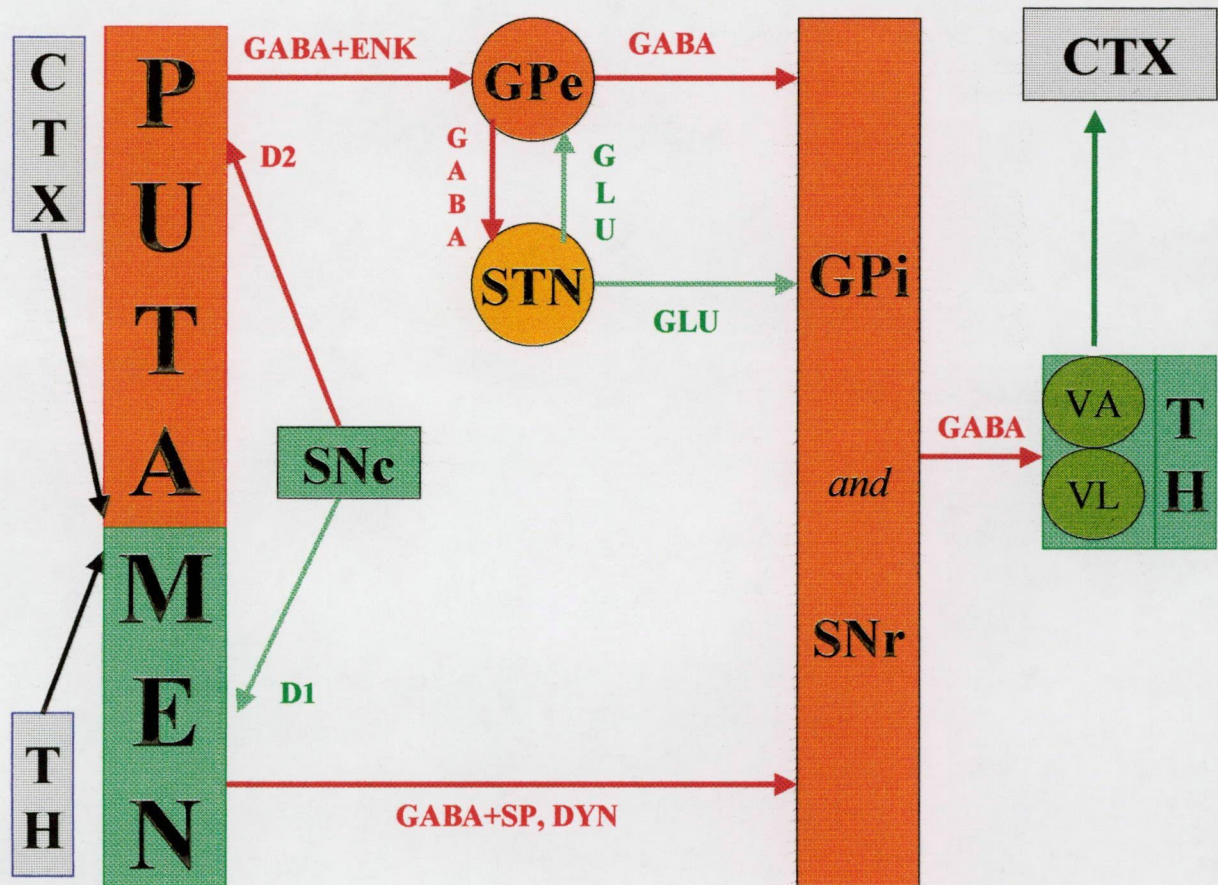


FIGURE 2. DIRECT AND INDIRECT PATHWAYS

Excitatory neurotransmitters are indicated in green, while inhibitory ones in red color. Also see list of abbreviations.

Today, the basal ganglia system is subdivided in three functional territories (i.e. group of circuits, rather than circuits). These are: the sensory-motor territory (putamen) projecting back to motor cortices (primary motor cortex, SMA, premotor cortex), the associative territory (dorsal caudate nucleus) projecting to the prefrontal cortex, and the limbic territory (ventral striatum) projecting to the anterior cingulate cortex and medial orbitofrontal cortices. There is considerable cross talk between these parallel circuits, making possible a higher level of integration between different CNS functions (Yelnik 2002).



Thus, basal ganglia play a crucial role in the coordination of a wide spectrum of CNS functions ranging from sensory and motor integration to cognitive and affective functions. Recording impulse activity of neurons in the basal ganglia shed light on the possible mechanisms employed by the basal ganglia in achieving this goal (Kropotov and Etlinger 1999). The basal ganglia-thalamocortical circuits become active only when a stimulus is attended or when a movement is voluntarily implemented. Thus they are involved in the process of selection of an appropriate sensory stimulus and in the selection of an appropriate motor action. This is realized by inhibitory, opponent neuronal mechanisms, suppressing inappropriate actions and initiating the selected one, in a "winner takes all" manner.

3. NEUROPSYCHIATRY OF THE BASAL GANGLIA

Considering the anatomy and physiology of the basal ganglia, it is not surprising, that its damage leads to many neurological and psychiatric diseases, and their presentation exceeds the limits of this thesis (for a review see: Ring and Serra-Mestres 2002).

The "classic" basal ganglia disorders are PD and related symptoms (progressive supranuclear palsy, multisystem atrophy), HD, Wilson's disease (copper deposition in the lentiform nucleus), Fahr's disease (calcium deposition in the basal ganglia), Gilles de la Tourette's syndrome (a combination of multiple motor and vocal tics).

However, there is mounting evidence that in many other diseases, malfunctioning of the basal ganglia is an important or possibly even the most important aspect: obsessive-compulsive disorder, depression, schizophrenia, addiction, attention-deficit hyperactivity disorder.

4. HUNTINGTON'S DISEASE

HD is a neurodegenerative disorder with autosomal dominant inheritance, characterized by choreoathetotic movement abnormalities, and cognitive and emotional impairment (Ross and Margolis 2001). The pathology of HD consists in atrophy in selective areas of the brain, the earliest and most severe neuronal loss affecting the MSN in the striatum.

The HD gene has been shown to be an expanded (>38) triplet repeat (CAG) sequence on chromosome 4, with longer repeats yielding an earlier age of onset (Group HD CR 1993, Duyano et al. 1993). Postmortem examination demonstrated a strong correlation between the extent of neuronal loss in the striatum and the number of nucleotide repeats (Furtado et al, 1996).

5. FOCAL LESIONS OF THE BASAL GANGLIA

There is much to be learned from humans whose brains are damaged by insults restricted to single anatomical structures. Because such lesions are rare, many reports of clinicopathological correlation are based on single cases or small series of patients. Bhathia and Marsden performed a meta-analysis of these papers, collecting 240 patients divided in two groups: those with small lesions only involving the basal ganglia and a group with larger lesions with additional involvement of the adjacent structures (Bhathia and Marsden, 1994). This comprehensive study revealed that isolated lesions of the basal ganglia (most of them vascular in origin) cause a wide variety of symptoms, from involuntary movements to acute confusion and aphasia. Lesions of the caudate nucleus most frequently cause behavioral or cognitive symptoms (abulia, disinhibition), while lesions of the lentiform nucleus predominantly cause dystonia.

6. SOMATOSENSORY EVOKED POTENTIALS IN BASAL GANGLIA DISEASES

SEPs are non-invasive, neurophysiological methods that make possible to record in different parts of the nervous system the electric activity evoked by stimulation of peripheral nerves (Osselton 1995).

Abnormalities of SEPs in HD patients were first described by Takahashi and Okada in 1972. All later studies revealed a drastic decrease in amplitude of the early cortical response to median nerve stimulation in spite of the differences in the methods and in the way the cortical components were defined (Oepen 1981, Jossiasen 1982, Ehle 1984, Noth 1984, Bollen 1985, Abbruzzese 1990, Yamada 1991, Töpper 1993). Conflicting results have been reported as concerns the latency and central conduction time (CCT): some authors observed a slowing of conduction (Takahashi and Okada 1972, Oepen 1981, Josiassen 1982, Abbruzzese 1990), while others noted normal values (Ehle, 1984, Bollen 1985, Yamada 1991, Töpper 1993). Though less extensively studied, a reduction in the amplitude of the early cortical components of the tibial nerve SEPs has also been reported (Noth 1984, Bollen 1985).

Since HD is not commonly associated with sensory symptoms, there is considerable controversy as to the cause of these well-documented neurophysiological changes. It was previously shown that the extent of striatal degeneration is proportional to the length of CAG expansion. Thus, we have approached the issue of striatal involvement in SEPs amplitude-decrease by determining the relationship between the severity of SEP changes and the length of the triplet repeat sequence in HD patients and their relatives at risk.

There is still much controversy about the SEPs alteration in PD. Several authors found a significantly reduced frontal N30, in spite of normal parietal components in PD patients (Rossini 1989, 1991, Onofrij 1995, Bostantjopoulou 2000). Since the frontal cortex receives a major input from the basal ganglia via the thalamic nuclei, it was hypothesized that a reduction in the N30 might be the consequence of an impairment of these inputs. However other authors could not replicate these findings (Mauguière 1993, Garcia 1995, Drory 1998) and even the origin (or origins) of N30 is not clear.

There are only few reports concerning N30 in focal intracerebral lesions, and none of them affecting the basal ganglia. Rossini et al. reported the selective elimination of the N30 on the side, where a meningioma was compressing the SMA (Rossini 1989). Selective loss of the frontal N30 component was also reported in 2 patients with precentral cortical lesions (Mauguière 1983) and three patients with focal capsular vascular lesions selectively deafferenting the prerolandic cortex (Mauguière 1991).

To investigate the suggested role of the basal ganglia in the generation of the N30 component, we recorded the median nerve SEPs in a patient with focal vascular lesion affecting only the striatum in one hemisphere.

7. EVENT RELATED POTENTIALS IN BASAL GANGLIA DISEASES

In 1996 Thorpe et al., recording event-related potentials (ERPs) during a visual categorization task, showed that a frontal negativity, at 150 ms after stimulus presentation (N150) was specific to the stimulus-category. The subjects had to decide, whether a photograph, flashed on for just 20 ms contained or not an animal. The category-specific N150 was thought to be the neurophysiological correlate of perceptual categorization and subsequent decisional processes.

Using a similar categorization-task ERPs (animal versus non-animal images) previous studies have shown specific alterations in PD patients. While in healthy subjects the evoked negativity at 150 ms post-stimulus presentation (N150) was higher for non-animal, than for animal images, this difference was abolished at all electrode sites for PD patients (Antal 2002 a, 2002 b). Because the degenerative process in PD is not confined to the nigrostriatal pathways but involve several other structures (dorsal raphe nuclei, locus coeruleus, nucleus basalis of Meynert), the N150 alteration might not solely reflect striatal pathology. Since these structures are unaffected in HD, it was tempting to use the same categorization-task ERPs in HD patients and their relatives at risk to check the role of the striatum in the

categorization/decision process. In addition, we performed the same categorization-task ERPs on a patient with vascular lesions of the right striatum.

In HD most of the previously published visual neurophysiological investigations focused on the characteristics of the (“classic”) P300 component of the ERPs, which is thought to reflect the attentional allocation and working memory updating. They have generally revealed amplitude reduction and disorganization of the components with or without latency shifts (Rosenberg 1985, Hömberg 1986, Münte 1997).

8. COGNITIVE DYSFUNCTION IN BASAL GANGLIA DISEASES

Cognitive impairment is a prominent feature of the pathologies affecting the basal ganglia (Ring and Serra-Mestres 2002). In PD patients, the most common problems are the slowing of mental processing (bradyphrenia), altered executive function as well as memory, and are in keeping with a subcortical pattern of dysfunction caused by disruption of frontosubcortical circuits and dopaminergic deficit in the mesocortical pathways. In HD, cognitive impairment is present early in the course of the disease. Slowing of cognition and difficulties with mental flexibility appear soon after the onset. Altered verbal fluency is one of the earliest cognitive deficits. Later on, cognitive impairment gradually worsens to a dementia of frontosubcortical pattern.

Adaptive behaviour requires the learning of stimulus-reward associations and the flexible shifting of response strategies. These functions are integrated in a widely used neuropsychological procedure, the Wisconsin Card Sorting Test (WCST) (Heaton et al. 1993). In the WCST, subjects are asked to sort test cards to one of four key cards that vary in shape, colour, and number. From the three perceptual dimensions, only one can be used for sorting (e.g. test cards should be matched to the key card with identical colour). Participants receive feedback to ascertain the categorisation rule, which shifts after a predefined number of successful decisions (e.g. from colour to shape). It has been demonstrated that patients with lesions to the dorsolateral prefrontal cortex (DLPFC) are less able to shift the sorting strategy (perseverative errors). However functional imaging studies showed that many other structures (including the caudate nucleus), besides DLPFC are activated during the test (Berman et al. 1995, Nagahama et al. 1996, Konishi et al. 1998, 1999). Early-stage HD patients were impaired in shifting cognitive set (Jossiassen et al. 1983).

The WCST can be decomposed into several domains with potentially separate cognitive and neuronal mechanisms. These can be systematically investigated using a multistage visual discrimination learning / attentional set-shifting paradigm (Downess et al.

1989). This task includes a series of two-alternative forced-choice visual discriminations. In the first stages, the discrimination of a simple stimulus pair and its reversal are requested. After an intradimensional shift phase (shift to another feature within the same perceptual dimension) subjects must adopt a new strategy by responding according to a previously ignored perceptual dimension. This extradimensional shift phase is believed to be the equivalent of the category-shift in the WCST. PD patients had difficulty throughout the task, while early stage HD patients showed a striking impairment specifically at the extradimensional shift phase (Downess et al. 1989, Owen et al. 1993, Lawrence et al. 1998).

Recently, the probabilistic classification learning (PCL) test has been introduced as a tool for investigating the parallel memory systems, including non-declarative learning functions related to the basal ganglia (Knowlton et al. 1996). In the PCL, subjects have to classify stimuli consisting of geometric shapes (cues) into two categories. Each cue is probabilistically related to one of the two categories. For example, the presence of cue A indicates that the stimulus belongs to the first category with a high probability, while cue B predicts the opposite category-membership. The probabilistic structure defeats the conscious memorisation of solutions. Some authors consider PCL a characteristic of striatally mediated, non-declarative, habit-based (i.e. stimulus-response reinforced) learning (Knowlton et al. 1996, Robins 1996). It has been shown that the PCL can be solved even if hippocampus and DLPFC are damaged, but not when basal ganglia functions are impaired: PD and HD patients showed marked abnormalities in the PCL task (Knowlton et al. 1994, 1996, Lawrence et al. 1998, Kéri et al. 2002). This suggests that the hippocampal/diencephalic explicit memory system and the DLPFC are dispensable for habit learning. Evidence from a recent, functional magnetic resonance imaging (fMRI) study supports this view. During the PCL task, increased blood-flow was detected in the bilateral frontal, occipital, and striatal regions, while the hippocampus was less active (Poldrack et al. 1999). It is noteworthy that striatal structures were active in both reversal learning and PCL paradigms, which supports the hypothesis that these stimulus-reward learning procedures share similar neuronal mechanisms.

Although nigral and striatal structures bear the brunt of the pathology in PD and HD respectively, the degenerative processes are not limited to these basal ganglia structures. Thus, it seemed intriguing to investigate these cognitive impairments in a patient with focal lesions confined to the right striatum.

III.

MATERIAL AND METHODS

1. SUBJECTS

Eleven patients with manifest HD showing typical cognitive and motor symptoms and six asymptomatic relatives were investigated. All of these subjects had a pathologic extension of the CAG repeat (shown by polymerase chain reaction) and no history of diabetes, alcoholism or mental deterioration (other than HD). The Ethics Committee of Szeged University Health Science Center approved the studies. All the subjects gave their informed consent, in accordance with the Declaration of Helsinki. Four patients were receiving tiapride and 1 patient was receiving haloperidol medication at the time of testing. The control group was recruited from the university staff and their relatives. None of the control subjects had neurological signs or symptoms and none of them was taking CNS-active medication. SEPs were recorded in 16 subjects displaying an extension of the CAG repeat (11 patients with manifest HD, 5 asymptomatic carriers) and 20 healthy controls. The ages of the HD patients varied between 21 and 80 years (mean = 48.45), the mean duration of the illness was 8.27 years (range: 1-17) and the median number of CAG trinucleotide was 45 (range 40-70). The mean age of the asymptomatic carriers (HDC) was 34.40 years (range: 27-44) and the median number of CAG trinucleotide was 44 (range 41-46). The mean age of the healthy control subjects was 37.20 years (range: 19-61). ERPs were recorded in 15 subjects with CAG expansion (9 HD patients, 6 asymptomatic carriers) and 14 healthy controls. They all fulfilled the following criteria: clear ocular media, normal intraocular pressure, and visual acuity better than 0.9 with or without correction. The age of HD patients (7 males, 2 females) was in the range of 28-60 years (mean = 48.66), the mean duration of the illness was 7.87 years (range: 1-14), the median number of the CAG trinucleotides was 45 (range: 40-51). The age of the HDC subjects (4 males, 2 females) was in the age range of 27-52 years (mean = 37.83) and the median number of CAG trinucleotide was 43 (range 41-46). The mean age of the healthy controls was 44.2 years (range: 30-60). The mean score in the Mini-Mental State Examination (MMSE) was 22.7 (range: 18-24) in the HC group, 29.2 (range: 28-30) in the HDC group and 29.6 (range: 28-30) in the control group. There were no significant differences between the control and HD, HDC subjects concerning their age and education level ($p > 0.05$).

In addition, we investigated a patient (ST) suffering form a rare form of cerebral vasculitis (granulomatous angiitis), proven by neuroimaging and laboratory data. ST was a 22-year-old right-handed Caucasian man (education: 12 years, WAIS-IQ: 106). Head MRI revealed that in the right hemisphere the lesions were confined to the striatum: head of the caudate nucleus (figure 3, bold arrow), anterior part of the putamen (figure 3, arrow). In the left hemisphere, there was a small lesion in the medial part of the thalamus and three small lacunar cortical infarcts (pre- and postcentral gyri, superior parietal lobe). Tests were performed before and after the steroid therapy.

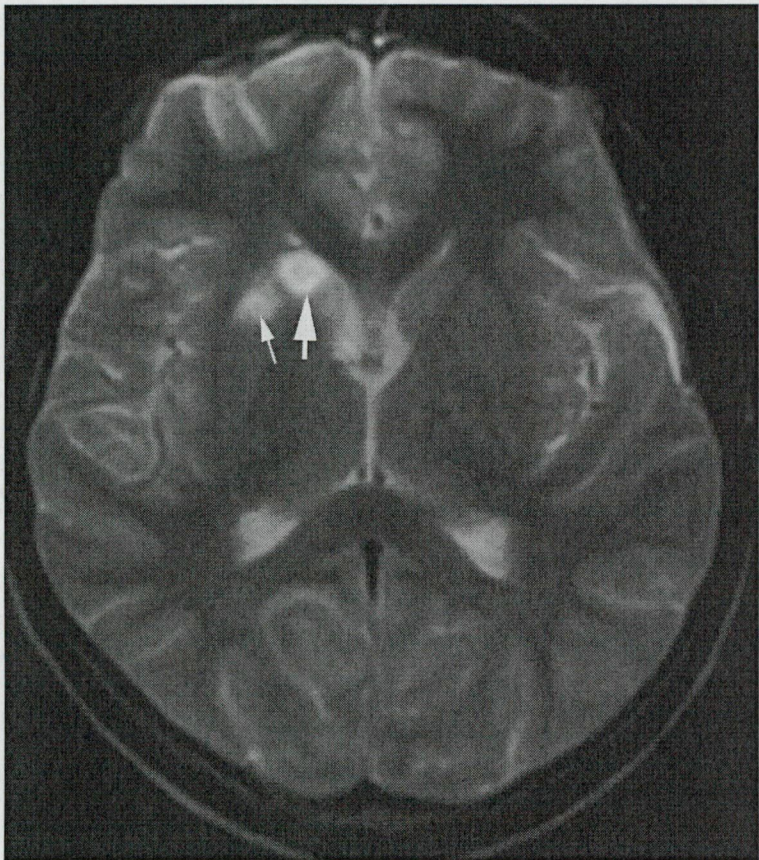


FIGURE 3. FOCAL LESIONS OF THE RIGHT STRIATUM

For the cognitive tests we used two control groups: one with parietal lesions and one of healthy volunteers. The control group with parietal lesions included three patients (mean age: 37.7 years (SD=25.5), mean years of education: 9.7 (SD=1.5), mean WAIS-IQ: 97.3). Two patients had bilateral parietal atrophy extending to the inferior and superior parts, and one patient had ischemic infarcts in the left parietal lobe, including the postcentral gyrus. One patient received anticonvulsant treatment (carbamazepine, 400 mg/day), and one patient

exhibited psychotic symptoms two years before the testing. The latter participant received combined antidepressant (citalopram, 20 mg/day) and antipsychotic (olanzapine, 15 mg/day) medication at the time of testing. The healthy control group comprised ten male volunteers without any history of neurological or psychiatric disorders (mean age: 21.9 years (SD=1.6), mean years of education: 10.3 (SD=1.8), mean WAIS-IQ: 103.9 (SD=5.9)).

2. SOMATOSENSORY EVOKED POTENTIALS (SEPs)

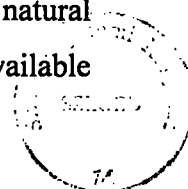
The subjects were lying supine, in a quiet, semi-darkened room. Square wave electrical pulses of 0.2-msec duration were applied at a stimulus frequency of 4 Hz to the median nerve at the wrist and subsequently to the posterior tibial nerve at the ankle. By means of unilateral stimulation, the left and the right sides were examined separately. The current intensity was adjusted so as to produce a visible twitching of the short muscles of the thumb or of the abductor hallucis after stimulation of the median nerve or of the tibial nerve, respectively.

The recording electrodes were placed at the posterior midline of the neck at C7 level (with an anterior cervical reference placed above the process of the thyroid cartilage) and on the scalp, over the contralateral hand field (2 cm posterior and 1 cm lateral to C3 and C4, according to the 10-20 International system) for the median nerve and 2 cm behind Cz for the tibial nerve. For all scalp recordings, an ipsilateral earlobe reference was used. The impedance was less than 5 k Ω . The signals were fed into amplifiers (Nihon Kohden Neuropack) and bandpass-filtered (5-3000 Hz). The sweep time was 100 msec. 1000 sweeps were averaged and at all stimulation sites the measurement was repeated once to check the reliability of the curves. Samples contaminated by artifacts such as movement or muscle potentials were effectively rejected by auto-rejection mode.

Peaks were identified with a cursor on the computer display. CCT was determined for the median nerve SEP as the difference between the peak latencies of parietal N20 and cervical N13, and for the tibial nerve SEP as the difference between those of cortical P40 and lumbar N22. We determined CCT because the three groups were not height-matched and CCT is unrelated to the height of the subjects. Peak-to-peak amplitudes for the median nerve at the frontal channel (P20-N30), at the parietal channel (P14-N20) and for the tibial nerve (P40-N50 and N50-P60) were determined.

3. EVENT-RELATED POTENTIALS (ERPs)

The stimulus battery included approximately 1000 color photographs of complex natural images, containing either an animal or a non-animal item (figure 4). All stimuli were available



from commercial databases and were matched for average luminance. All stimuli subtended a vertical visual angle of 10° and a horizontal visual angle of 15° from a viewing distance of 1 m. A small fixation dot was present in the middle of the video screen (Studioworks 57i), controlled by an IBM Pentium PC. The luminance of the stimulus area (80 cd/m²) and the background luminance (8 cd/m²) were held constant throughout the experiment.

Participants were asked to fixate the small dot in the middle of the screen. The subject with pressing one of the two response buttons initiated the sequence of trials. One trial consisted of the presentation of a single stimulus for 26 ms. Subjects were asked to decide whether the presented image contained an animal (target) or a non-animal (distracter) item with pressing the appropriate button within 1500 ms (figure 4). The interstimulus interval was 2 s. Stimuli were presented in a randomized order. The probability of target and distracter items were equal (50%). The task consisted of 500 trials in two separate blocks of 250 trials. No images were presented twice in order to avoid practice effects. A training block was given before the test to ensure that each subject understood the task. None of the subjects reported any fatigue effect after the presentation of the two blocks.

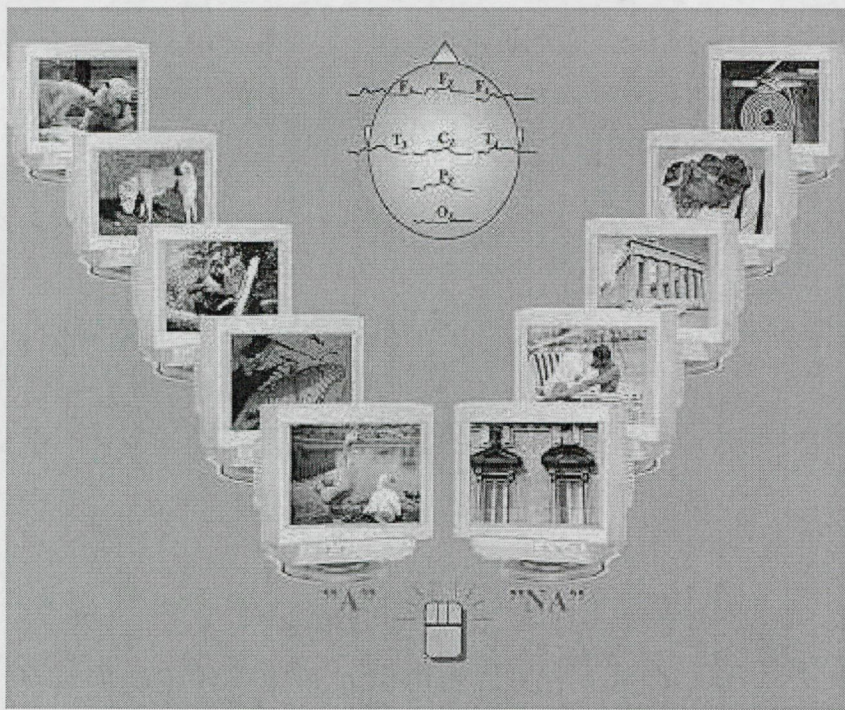


FIGURE 4. SCHEMATIC REPRESENTATION OF THE ANIMAL/NON-ANIMAL VISUAL CATEGORIZATION-TASK ERPs

For the neurophysiological recordings, gold cup electrodes with a diameter of 6 mm were used, which were placed in accordance with the international 10-20 system. The primary evoked potential was recorded at Oz referred to an electrode positioned at 70% of the distance between inion and nasion. ERPs were recorded at Fz, Cz, Pz, F3, F4, T3, and T4 referred to linked mastoids (Rlm). The ground electrode was located on the forehead. Signals were amplified 10,000 times. Data were collected and analyzed off-line by an IBM-compatible PC. Filters were set at 0.1 and 70 Hz. A notch filter was used to remove 50 Hz interference. The sampling rate was 1,000 Hz. Individual potentials were baseline corrected on the basis of a 100 ms prestimulus period. The analysis time of poststimulus period was 500 ms. In order to control eye movements, a concurrent electrooculogram (EOG) was recorded. Automatic artifact rejection was used to remove trials with amplitude higher than 50 μ V.

Mean amplitudes were measured between 150 and 250 ms (N150) following stimulus onset. To test the normality of distribution, data were entered into Kolgomorov-Smirnov analyses. Mean amplitudes were analyzed with 3 (group: controls vs. HD patients vs. HDC subjects) \times 2 (stimulus: target vs. distracter) \times 7 (electrode sites) repeated measures analyses of variances (ANOVAs). For post-hoc comparisons, Fisher's LSD tests were used. To control type II errors, Greenhouse-Geisser corrections were included.

4. COGNITIVE TESTS

Besides the IQ (Wechsler, 1981), the neuropsychological evaluation included the following tests: (1) WCST (attentional set-shifting), (2) PCL (habit learning and episodic memory), (3) digit span forward and backward (working memory), (4) word span and alphabet span (working memory), (5) phonological and semantic fluency (verbal initiation and generation), (6) Benton Facial Recognition Test and Object Decisions (visual perception), (7) Association Match and Category Match (semantic memory). The first five tests were administered before and after the steroid therapy. The time interval between the pre- and post-treatment assessments was one month. Similarly, these tests were repeated in the healthy control subjects after one month of initial assessment.

WCST. The procedure is described in details elsewhere (Heaton et al. 1993). Briefly: subjects are asked to sort test cards to one of four key cards that vary in shape, colour, and number (figure 5). From the three perceptual dimensions, only one can be used for sorting (e.g. test cards should be matched to the key card with identical colour). Participants receive feedback to ascertain the categorisation rule, which shifts after a predefined number of successful decisions (e.g. from colour to shape). The number of categories completed and the

number of perseverative errors were the dependent measures.

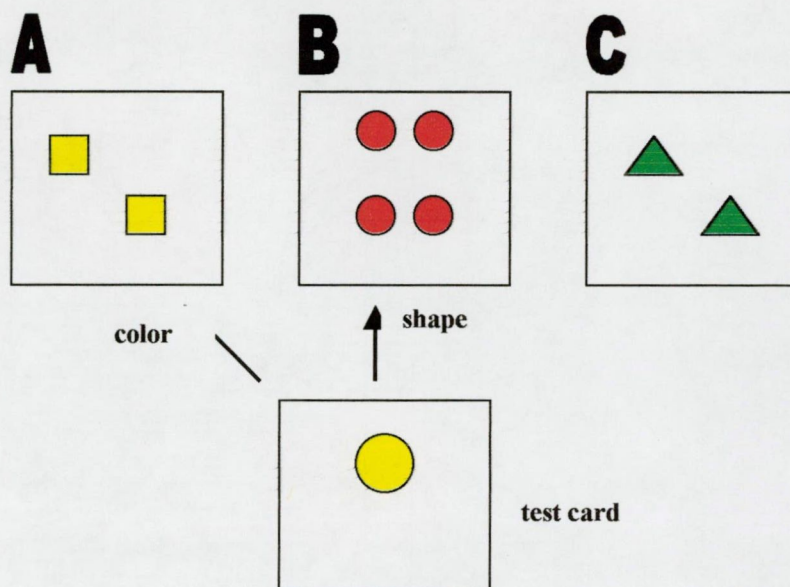


FIGURE 5. WISCONSIN CARD SORTING TEST (WCST)

PCL. To assess the functioning of the striatal habit learning system, the PCL paradigm was used. In the weather prediction task (figure 6), which was a pen-and-paper version of the original version (Knowlton et al, 1994, 1996, Kéri et al. 2002), the participant was asked to decide whether a pattern of cues predicted category 1 (rain) or category 2 (sunshine). In each set, cues (simple geometric shapes) were included. Each cue was associated with a particular category with a certain probability (figure 6). In each trial 1, 2, or 3 cues were presented. The cues were printed on cards and their left-to-right sequence was randomised. The participant was asked to decide whether the cue(s) indicated rain or sunshine. The decision time was limited to 5 sec. If no response was made, the subject was asked again to categorise the stimulus. After each trial (response), the examiner provided verbal feedback (stating whether the cue represented rain or sunshine). Altogether, 100 trials were included (10 blocks of 10 trials). In the case of ST, the test was repeated four times with different sets before and four times after the therapy. In the case of each patient with parietal lesions, the test was repeated with two different sets. Data from normal control participants showed that equal learning effects could be obtained using the different sets. Performance was defined as the percentage of correct responses. Cue patterns associated with rain and sunshine with equal probabilities were excluded from the data analysis.

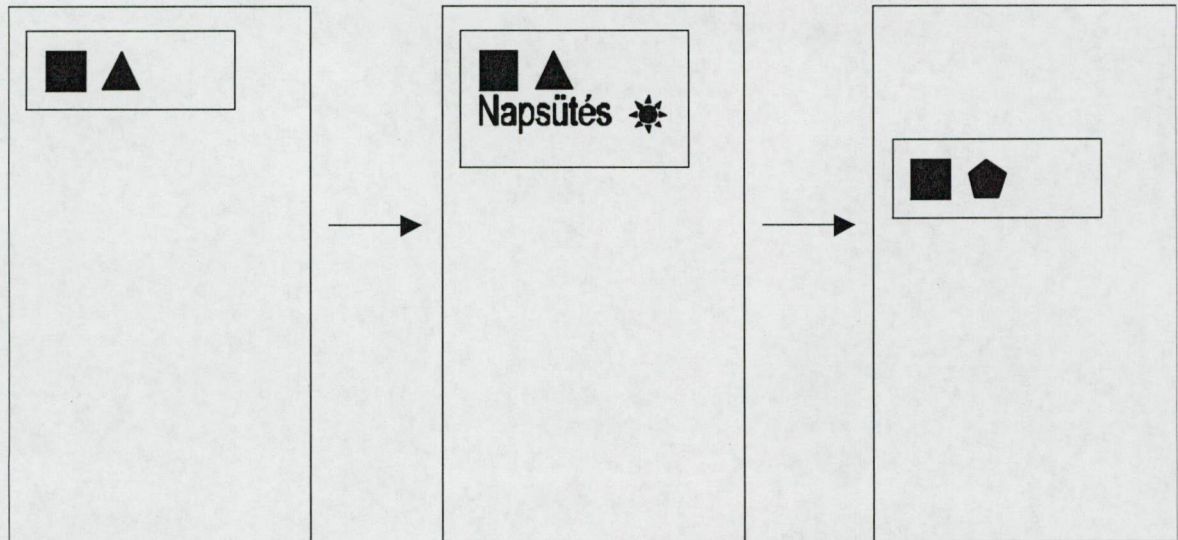


FIGURE 6. PROBABILISTIC CLASSIFICATION LEARNING

“Napsütés” is the Hungarian for sunshine, which is one of the two categories in the task.

Explicit episodic memory for the habit learning task was assessed with a multiple-choice task, including questions about the cues, the layout of experimental environment, and the training episode (chance level: 25%).

Digit span forward and backward. In the digit span forward test of the WAIS (Wechsler, 1981), increasingly longer strings of numbers are recalled (1-9 letters). In the backward version, subjects repeat the numbers in reverse order. Span length is defined as the numbers of digits recalled correctly before two strings of the same length were failed.

Word span forward and alphabet span. In the word span test, increasingly longer strings of one syllable, high-frequency words are recalled (2 to 8 words) (Paivio et al. 1968). In the alphabet span task, words are recalled in alphabetical order (Craik, 1986). The length of word strings was calculated in the same manner as in the digit span task.

Phonological and semantic fluency. For the assessment of phonological fluency, the Controlled Oral Word Association Test was used (Benton and Hamsher 1976). In this test, subjects are asked to retrieve as many words as possible beginning with letters F, A, and S for 1 min each. Participants were requested to avoid proper names and places. The dependent measure was the mean number of words generated over 1 min ($[F + A + S] / 3$). Errors were excluded. In the assessment of semantic fluency, the task was to generate words belonging in the category of animals and furniture for 1 min each (Randolph et al. 1993). The dependent

measure was the mean number of words generated ($[\text{category A} + \text{category B}] / 2$). Errors (repetitions and words outside the categories) were excluded.

Benton Facial Recognition Test and Object Decisions. These tests were designed to investigate visual perception. In the Benton Facial Recognition Test, subjects are required to match faces shown under different angles and different shadowing (Lezak 1995). In the Object Decision test, pairs of pictures of the same objects are presented that are differing only in one detail (e.g. a bear with rounded or pointed ears) (Goldenberg and Karlbauer 1998).

Association Match and Category Match. These tests were designed to investigate semantic memory. In the Association Match of the Pyramids and Palm Tree Test, a target picture is shown with two choice pictures. One of the choice pictures is functionally associated with the target picture (Howard and Patterson 1992). In the Category Match version, choice pictures must be matched by superordinate category rather than by functional associations (Goldenberg and Karlbauer 1998).

IV.

RESULTS

1. PRIMARY PERCEPTION AND CORTICAL EXCITABILITY (SEPs)

SEP amplitudes and CCT in HD and HDC

Initial analyses of variance (ANOVAs) and Mann-Whitney U tests revealed no significant difference between the median and tibial nerve SEP data obtained from the left- and right-sided recordings ($p>0.6$). Similarly, there was no laterality-specific difference between any of the three experimental groups ($p>0.7$). Therefore, the SEP data from both sides were averaged for further between-group comparisons.

Table 1 shows median and tibial nerve SEP parameters for the HD patients, the HDC subjects and the healthy control subjects. Figure 7 shows SEP recordings on a control subject and on a HD patient

	HD (n=11)	HDC (n=5)	Controls (n=20)	t score (HD vs. controls)	P (HD vs. controls)	t score (HDC vs. Controls)	P (HDC vs. controls)
CCT N13-N20	5.94 (1.13)	6.21 (0.64)	5.64 (0.65)	-1.28	0.2074	-2.37	0.0218
P14-N20 amplitude	1.53 (1.69)	2.26 (1.01)	3.06 (1.69)	4.57	0.00003	2.36	0.0223
P20-N30 Amplitude	0.91 (1.01)	1.56 (0.86)	2.08 (1.02)	4.36	0.00005	1.49	0.1423
CCT* N22-P40	-	16.41 (1.67)	18.15 (15.20)	-	-	0.33	0.7358
P40-N50 amplitude	0.19 (0.48)	1.33 (0.76)	2.67 (1.44)	7.82	<0.00001	2.84	0.0065
N50-P60 Amplitude	0.19 (0.45)	1.44 (0.65)	3.05 (1.66)	7.88	<0.00001	3.00	0.0043

Table 1.

Mean (SD) central conduction time (CCT) (msec) and peak-to-peak amplitude (μ V) of the median and tibial nerve SEP cortical components in the patients with Huntington's disease (HD), the asymptomatic mutation carriers (HDC) and the healthy control subjects.

**The mean CCT is not indicated for the HD group, because most of the patients (n=9) demonstrated no detectable P40 component, and therefore CCT could not be determined.*

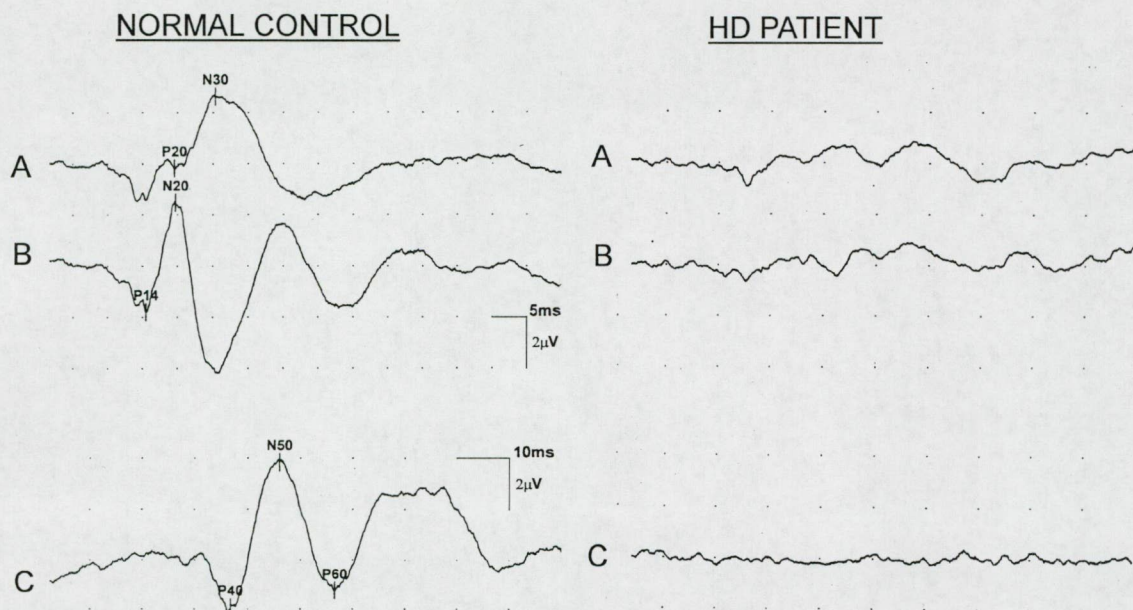


FIGURE 7.

Median nerve SEP: recording from frontal (A) and parietal (B) leads. In the normal subject the cortical components show a distinct pattern, while in the HD patient the cortical responses are markedly reduced. Cortical SEP recording after tibial nerve SEP (C); in the HD patient the cortical component (P40-N50-P60) is absent.

For the median nerve SEPs, comparisons between the HD patients and the control subjects with Student t-tests indicated significantly reduced peak-to-peak amplitudes (P14-N20 and P20-N30) ($p < 0.001$ for each comparison). There was no significant difference as concerns CCT ($p = 0.2074$) (Table 1). When the HDC subjects and the controls were compared with t-tests or Mann-Whitney U tests, CCT and the P14-N20 amplitude also demonstrated significant alterations in the HDC group ($p < 0.05$ for each comparison). However, when the significance level was corrected for type 1 errors (Bonferroni), these effects were no longer observed.

For the tibial nerve SEPs, we noted a more robust difference between the three groups (Table 1). In a majority of HD patients (9 of 11), no detectable P40-N50-P60 was present, in spite of a normal N22 (lumbar) component. The HDC - control difference was also larger than that observed for the median nerve amplitudes. To further elucidate the hypothesis that the tibial SEP amplitudes were more severely affected, a group (HD patients vs. carriers vs.

controls) by SEP type (median vs. tibial) ANOVA was performed. This analysis revealed the main effects of group (Rao's $R(4,136)=18.28$, $p<0.0001$) and SEP-type (Rao's $R(2,68)=17.06$, $p<0.0001$). The interaction was also significant (Rao's $R(4,136)=3.82$, $p<0.01$). Scheffé's post hoc tests demonstrated significant amplitude reductions in the HD patients ($p<0.0001$) and in the HDC group ($p<0.01$) in comparison with the controls. The HD patients had smaller amplitudes as compared with the carriers ($p<0.05$). The tibial SEP amplitudes were more severely affected than the median SEP amplitudes when the HD patients and the controls were contrasted (Rao's $R(2,68)=7.63$, $p<0.005$). However, this effect was observed merely as a slight tendency when the carriers and the controls were contrasted ($p=0.16$).

Relationship between SEP parameters and CAG repeat length

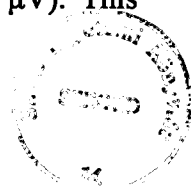
To investigate the relationship between the neurophysiological data and the genetic factors, Spearman's correlation coefficients were calculated between the SEP parameters and the number of CAG repeats measured in the HD patients (median: 45, min: 40, max: 70) and in the HDC group (median: 44, min: 41, max: 46). This analysis revealed that smaller N20/P14 and N30/P20 amplitudes were associated with a higher number of CAG repeats ($R=-0.61$, $p=0.012$ and $R=-0.56$, $p=0.023$, respectively). All other correlation remained below the level of statistical significance ($p>0.1$).

Effects of clinical and demographic parameters

The duration of the illness correlated only with CCT ($R=0.75$, $p=0.029$), and not with other SEP parameters. It is of particular interest that we found no significant correlation between the age and the measured SEP parameters ($p>0.1$), because in this study the control group was younger than the patient group. For exclusion of the potentially confounding effect of age, only age-matched control subjects were included in a separate control analysis. The result remained the same, suggesting that the between-group effects were not due to age differences. Similarly to previously published data (Noth 1984, Bollen 1985, Abbruzzese 1990), we obtained the same results when the medicated patients were excluded. Finally, there was no significant difference between the male and female participants ($p>0.6$).

SEPs in focal lesions of the striatum

In patient ST (figure 8), stimulating median nerve on the left side (contralateral to the striatal lesions) evoked no identifiable frontal components (P20, P22, N30) and a parietal component of slightly reduced amplitude (P14-N20 = 1.98 μ V). Stimulating the right side resulted in normal cortical components (P20-N30 = 2.00 μ V, P14-N20 = 2.60 μ V). This



patient was reexamined, using additional recording sites (C3, C4, P3, P4) too, but the frontal components, on the affected side were missing even in these recordings.

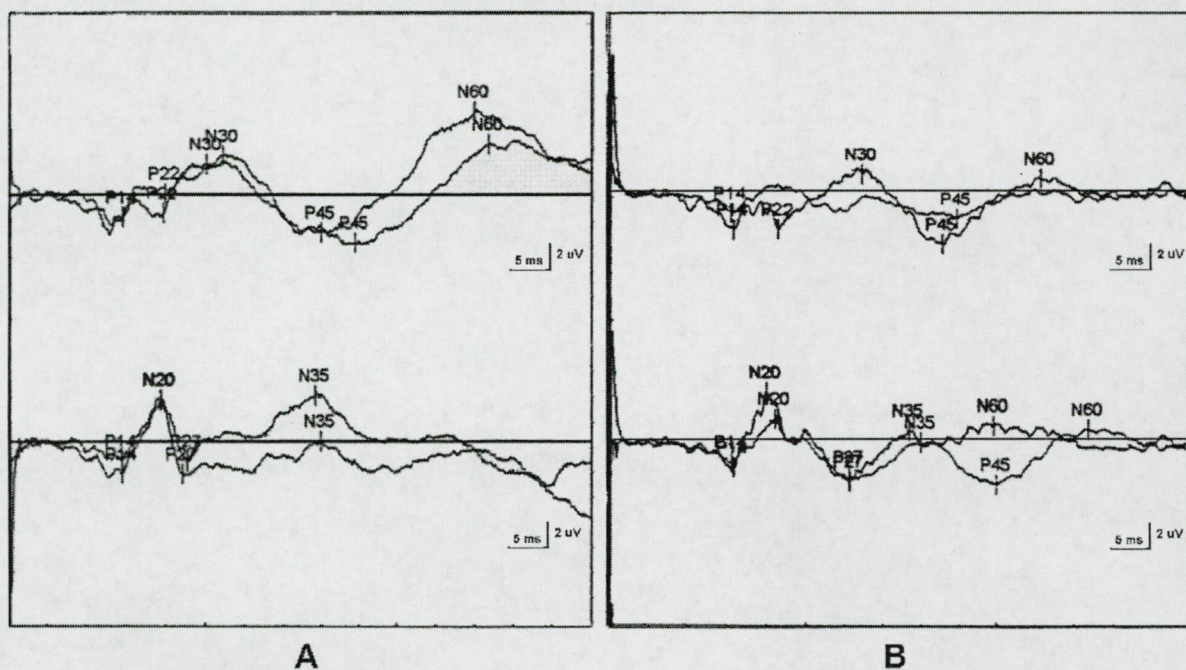


FIGURE 8. MEDIAN NERVE SEPs.

Recordings from right and left sides are shown superimposed. A: healthy control. B: a patient with focal striatal lesions on the right side. Upper tracings: frontal recordings. Lower tracings: parietal recordings. Straight line represents the baseline.

2. PERCEPTUAL CATEGORIZATION/DECISION PROCESS (ERPs)

P100 and N150

Concerning the primary occipital component (P100), there was no significant difference between the control subject and HD patients ($p > 0.1$) (Table 2.). However, the amplitude of N150 component was smaller for both kinds of stimuli in the HD group than in the control and in the HDC group. Comparing the control and the HD group, there were main effects of stimulus ($F(1, 22) = 5.63$, $p < 0.03$, $\epsilon = 1.00$) and electrode site ($F(6, 132) = 13.3$, $p < 0.0001$, $\epsilon = 0.495$). The effect of group almost reached the significance level ($F(1, 22) = 4.05$, $p = 0.056$). The interactions between group and electrode site ($F(6, 132) = 4.604$, $p < 0.003$, $\epsilon = 0.495$) were also significant. Other two-way interactions remained non-significant (group and stimulus: $p = 0.56$; stimulus and electrode-site: $p = 0.14$). The three-way interaction was almost significant ($F(6, 132) = 2.03$, $p = 0.06$, $\epsilon = 0.61$).

	P100 Amp. (SD) μV	N150 amp. diff. at Fz μV	N150 amp. diff. at Cz μV	N150 amp. diff. at Pz μV	N150 amp. diff. At F3 μV	N150 amp. Diff. at F4 μV	N150 amp. diff. at T3 μV	N150 amp. diff. at T4 μV
Control	9.22 \pm 5.2	-1.67	-1.82	-1.27	-1.25	-1.58	-1.6984	-1.67
HD	8.58 \pm 2.9	-1.25	-0.69	-0.94	-1.06	-1.14	-0.14	-0.27
HDC	10.75 \pm 3.2	-1.33	-1.25	-1.66	-0.875	-1.29	-1.54	-1.22

Table 2.
Mean P100 amplitude and N150 amplitude differences (subtracting animal from non-animal ERPs) in the control, HD and HDC subjects.

Fisher LSD tests revealed that non-animals elicited more negative responses than animals at each electrode site ($p<0.015$). Within-group comparisons indicated that these more negative non-animal components only were present in the control group at all electrode locations ($p<0.0001$). Conversely in the HD group the non-animal items failed to trigger a more negative component at the two temporal sites (T3, T4, $p=0.68$); at all other electrode sites the non-animal components were more negative than the animal components ($p<0.05$) (figure 9).

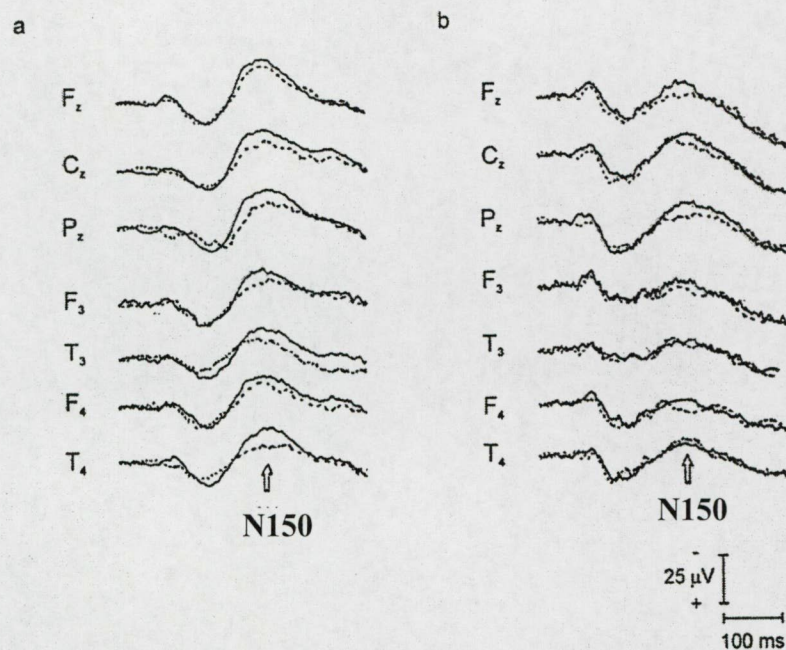


FIGURE 9. GRAND AVERAGE ERPs OF THE CONTROL (a) AND THE HD GROUP (b)

In the patient with focal lesions of the striatum, the P100 was normal. However, in contrast to the controls, the non-animal images failed to evoke a larger N150 than animal images (target-distracter N150 difference smaller than $-0.5 \mu\text{V}$) at all electrode sides.

Comparing the control and the HDC group the three way ANOVA showed main effect of stimulus ($F(1, 19)=17.056$, $p<0.0006$) and electrode localization ($F(6,114)=9.37$, $p<0.0001$, $\epsilon=0.48$). The other effects and interactions remained non-significant.

The CAG repeat length and the duration of the disease did not correlate with the amplitude of N150 component (Spearman, $r=-0.10-0.56$, $0.05-0.3$, respectively).

3. COGNITIVE FUNCTIONS

Neuropsychological tests

In the case of four measures (WCST categories completed and perseverative errors, digit span backward, alphabet span), the performance of ST was impaired, falling outside the normal range (control mean ± 1 SD). No other impairments were observed. After the steroid therapy, these impairments showed a marked improvement (Table 3).

Habit-learning (PCL)

Before treatment, a subjects (ST vs. controls vs. patients with parietal damage) by trial blocks analysis of variance (ANOVA) showed main effects of subjects ($F(2,17)=6.34$, $p<0.01$) and trial blocks ($F(4,68)=4.84$, $p<0.002$). The two-way interaction was not significant ($p>0.5$). Tukey's HSD tests indicated that both ST and the parietal patients showed lower overall performances in comparison with the controls ($p<0.05$), whereas there was no significant difference between ST and the parietal patients ($p>0.5$). However, analyses of linear trend indicated that both the controls ($F(1,17)=30.38$, $p<0.001$) and the parietal patients ($F(1,17)=24.60$, $p<0.001$) increased their performance as a function of trial blocks, whereas this effect was not present in ST before or after the treatment ($p>0.21$) (Figure 10). In addition, when ST and the parietal patients were contrasted for a linear trend, there was a significant interaction ($F(1,17)=5.38$, $p<0.05$). No such interaction was found when the parietal and the control participants were compared ($p>0.5$).

After the completion of additional 50 trials, the performance of the controls was 69.0% (SD=7.4), while that of ST was 67.5% (SD=9.6) before the treatment and 65.0% (SD=5.8) after the treatment. Separate t-tests showed that these data were not different from the control value ($p>0.3$), and no individual data were below the cut-off score after the

completion of all 100 trials. In the declarative memory test, the control mean was 89.0 % (SD=11.0). ST's performance was 85% before the treatment and 80% after the treatment.

	CONTROL 1	CONTROL 2	ST BEFORE TREATMENT	ST AFTER TREATMENT
Number of categories completed (WCST)	5.6 (0.5)	5.8 (0.4)	3	5
Perseverative errors (WCST)	6.7 (1.3)	6.5 (1.4)	31	9
Digit span forward	7.4 (0.5)	7.6 (0.7)	7	7
Digit span backward	6.9 (0.6)	6.8 (0.6)	4	7
Word span	6.1 (0.9)	6.1 (0.7)	6	6
Alphabet span	5.3 (0.5)	5.2 (0.8)	3	5
Phonological fluency	15.8 (2.3)	15.9 (1.7)	15	14
Semantic fluency	20.2 (2.1)	19.9 (2.8)	19	21
Facial Recognition	-	-	53/54	52/54
Object Decision	-	-	23/25	24/25
Association Match	-	-	50/52	51/52
Category Match	-	-	17/18	18/18

Table 3. Neuropsychological performance of ST and the matched control subjects

In the two testing sessions of the control participants (CONTROL 1 and CONTROL 2), Wisconsin Card Sorting Test (WCST), digit span, word span, alphabet span, and fluency tests results depict mean values (SD). In the case of Facial Recognition, Object Decision, Association Match, and Category Match tests the first number refers to the score obtained from ST, while the second number indicates the maximal score. Values for ST are shown before and after the steroid therapy

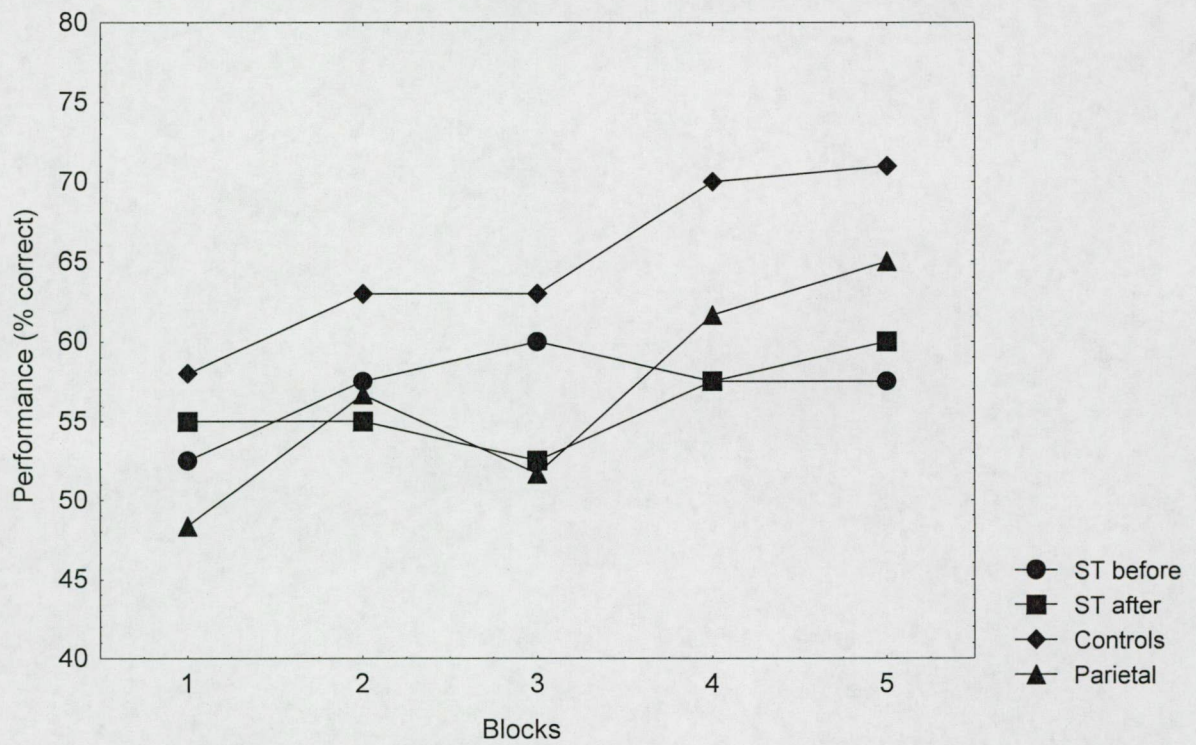


FIGURE 10. The performance of ST, healthy controls, and patients with parietal lobe lesions in the probabilistic classification learning procedure.

V.

DISCUSSION

1. PRIMARY PERCEPTION AND CORTICAL EXCITABILITY (SEPs)

In accordance with previously published data, in HD patients we demonstrated a significant reduction in the early cortical component amplitudes of the median and tibial nerve SEPs. There has been considerable controversy concerning the explanation of such SEP alteration in HD, since sensory changes are not typically part of the HD symptomatology. Neuronal loss in the thalamus and the somatosensory cortex and the effects of medication were also taken into consideration.

We observed a significant correlation between the CAG repeat length and the severity of the amplitude reduction of both the frontal and parietal components of the median nerve SEPs, with longer repeats being associated with a more pronounced decrease in amplitude. Post-mortem studies revealed a strong correlation between the repeat length and the severity of neuronal loss in the striatum (Furtado 1996). Therefore, it is highly possible that the SEP alterations are caused by the pathological process in the striatum, probably by affecting the cortical excitability through subcortical neuronal circuits passing through the basal ganglia. This hypothesis is supported by the results of PET studies (Kuwert 1993), showing a correlation between the decrease in striatal glucose consumption and the extent of SEP alteration, and additionally by animal models (Schwarz 1992), in which excitotoxic damage to the basal ganglia alone was sufficient to induce the SEP changes.

Conflicting results have been published concerning the SEP latencies. In contrast with several authors (Takahashi 1972, Oepen 1981, Josiassen 1982, Abbruzzese 1990), we found normal CCT in the HD patients and also in the HDC group. The lack of a correlation between CCT and the length of the nucleotide repeat also suggests that action potential conduction is unaltered in HD.

In the present study the tibial SEP was found to be more sensitive than the median SEP, the reduction in the tibial SEP cortical component amplitudes being the only significant neurophysiological change observed in the HDC group. Although this alteration has been described in previous reports (Noth 1984, Bollen 1985), our study demonstrated more severe alterations. The major methodological difference was that we used an ipsilateral auricular reference instead of Fz, which might account for the slightly different results. The severe

alterations in the cortical components of the tibial SEP in most of the HD patients (in 9 of the 11 patients the components were absent) explains why there was no mathematically demonstrable correlation between the nucleotide repeat length and the tibial SEP alterations.

This is the first study to report a relationship between the severity of neurophysiological abnormalities and the extent of a trinucleotide repeat extension, the genetic background of several inherited neurodegenerative disorders.

In the patient with focal lesions in the right hemisphere confined to the striatum, we found selectively abolished frontal components and a parietal component with decreased amplitude, on the affected side. In contrast to patients with neurodegenerative diseases, in ST we had the opportunity to study the consequences of lesions limited to certain anatomic structures. These data further emphasize the important role of the striatum in the generation of the median nerve SEPs, especially in the formation of the frontal components.

2. PERCEPTUAL CATEGORIZATION/DECISION PROCESS (ERPs)

Using a visual categorization (animal/non-animal) task, we have found that in HD patients, the non-animal versus animal difference in the N150 component was only altered at the temporal electrode sites. In previous studies this alteration was demonstrated at all electrode sites in PD patients, but at none of the electrode sites in patients with Alzheimer's disease (Antal et al. 2002a, 2002b), where a widespread cortical pathology is well known. Based on these findings we attributed the alterations in the N150 component found at the temporal electrode sites to the pathologic changes in the basal ganglia. Of note is, that neuroanatomic studies (Middleton and Strick 1996) showed a closed loop connection between the basal ganglia and the temporal cortex, which influences higher order visual processing. Thus the alteration of the N150 component at the temporal electrodes might be a consequence of the malfunctioning in these circuits. PD and HD affect basal ganglia functions in very different ways: in PD the degeneration of nigro-striatal dopaminergic circuitry occurs beginning in the putamen, while in HD the striatum is degenerated itself (in a dorsal-to-ventral and medial to lateral manner) starting in the caudate nucleus (Joel 2001). Although the striatum suffers the greatest damage, other neuronal regions are affected to varying degrees, such as the cortex, globus pallidus, subthalamic nucleus, amygdala, thalamus and hypothalamus. The substantia nigra, pars compacta, the nucleus basalis of Meynert, the dorsal raphe and the locus coeruleus afferent projection systems seem to be spared in contrast to PD. Thus, our results suggest that different degenerative processes of the basal ganglia can cause distinct alterations of the cortical excitability. This is further supported by similar, but not

identical neurophysiological changes (SEPs and ERPs) found in a patient with focal vascular lesions of the striatum.

In the HD group the N150 component was diminished for both kind of stimuli. This is intriguing especially in the light of normal primary occipital component (P100). We hypothesize that these N150 changes are related to the decreased cortical excitability due to the dysfunctional cortico-basal ganglia–cortical circuits. In previous studies, several authors reported a reduction in the P100 amplitude (Oepen et al. 1982, Josiassen et al 1984, Hennerici et al. 1985). The difference between these and our findings (normal P100) could be explained by the difference in the types of stimuli: checkerboard pattern reversal in the previously published articles versus complex natural scenes in our study.

The lack of relationship between the changes in the categorization/decision process and the CAG repeat length is not surprising since it was shown that cognitive symptoms are unrelated to the repeat length (Ross et al. 2001) but our sample was too small for a definite conclusion about this aspect.

Asymptomatic HDC mutation carriers in this ERPs study were not different from control subjects concerning the N150 component. However the number of subject in this group was too small to draw a conclusion. Repeated measurements in a larger population may help us to clarify this aspect.

This is the first study that described in HD patients, a neurophysiological evidence for impairment of the early perceptual processes in a visual categorization/decision task. We have found that although HD and PD are widely used models of basal ganglia dysfunction in humans, HD subjects showed a different pattern of impairment from what was observed in PD patients.

Defining specific neurophysiological alterations corresponding to distinct pathologic changes in the basal ganglia may consistently help us to a better understanding of the normal and abnormal functioning of the affected neural circuits.

3. COGNITIVE FUNCTIONS

Neuropsychological examination of ST revealed selective impairments in attentional set-shifting (WCST perseverative errors), digit span backward, alphabet span, and habit learning (PCL). By contrast, general intellectual functions, short-term memory for digits and words, verbal fluency, episodic and semantic memory, and object recognition, were unaffected. After steroid therapy, attentional set-shifting and related functions showed robust improvement (probably due to an increase in blood flow in the compromised vessels).

whereas habit learning remained severely impaired. The alteration of attentional set-shifting and related functions cannot be attributed solely to basal ganglia pathology, since they improved after the steroid therapy in spite of the definite (irreversible) nature of the striatal lesions (as shown by repeated MRI). However, the alteration in habit learning (PCL) might indeed be the consequence of striatal lesions, since it remained unchanged after the therapy. PCL impairment cannot be explained by the parietal lesions, because the patients with damaged parietal lobes showed normal learning rates in the PCL task. It is unlikely that the therapy led merely to a global improvement, because attentional set-shifting is more difficult than the PCL-type tasks for normal participants (Roberts et al. 1998).

In the early phase of PCL (1-50 trials) there was an obvious deficit in habit learning, whereas episodic memory for cues and experimental circumstances was spared. In later phases of the PCL (50-100 trials) ST's performance increased, which suggests that he used the spared explicit memory functions to encode stimulus-response patterns similarly to patients with Parkinson's disease (Knowlton et al., 1996). While executive functions robustly improved after the steroid therapy, ST was still unable to learn stimulus-response habits. Overall, these data support previous observations from patients with amnesia, Parkinson's disease, and frontal lobe lesions (Knowlton et al. 1994, 1996), suggesting that executive (attentional set-shifting) dysfunction can be independent of habit learning problems, although dual deficits often occur. In addition to the neuropsychological evidence, a number of studies using animal models indicated that set-shifting and reversal learning are mediated by separate neuronal systems. Set-shifting is related to the dorsal fronto-striatal system, whereas reversal learning is related to ventral fronto-striatal circuits (Divac et al. 1967, Jones and Mishkin 1972, Dias et al. 1996, Li and Shao 1998, Ferry et al. 2000).

In connection with our interpretation, two important limitations must be mentioned. The lesions were restricted to the basal ganglia, only in one hemisphere, which raises the possibility that lesions outside these structures in the other hemisphere may have contributed to his dysfunctional performance. We tried to exclude this possibility by the assessment of patients with parietal damage and found that these patients showed normal learning rates in the PCL task. The possible role of the left medial thalamic infarct was not specifically investigated. Although this lesion was small, it is possible that it may have induced a disconnection in the left fronto-striato-thalamo-cortical circuits, specifically contributing to the set-shifting and habit learning anomalies. It must be also taken into consideration that vasculitis potentially results in brain dysfunction not detected by MRI. However, the presence

of a diffuse cerebral lesion with a generalised cognitive impairment was clearly excluded, since ST's impairment was selective for a subset of neuropsychological tests.

4. MANY INTERCONNECTED CIRCUITS

Although the basal ganglia have long been viewed as playing a central role in motor control, there is increasing evidence, that these structures are essential for synchronisation of neural circuits related to many other functions of the brain. This is not surprising, given the fact, that the basal ganglia receive inputs from all cortical areas, and in turn, affect the cerebral cortex via their thalamic projections.

In the last 16 years, the most dominant view of the cortico-basal ganglia-thalamo-cortical circuits was the one pioneered by Alexander et al. According to this, the circuits are organised in a parallel manner and remain structurally and functionally segregated from one another (Alexander et al. 1986). They identified five parallel circuits: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and limbic / anterior cingulate.

Our results showed, that damage to the basal ganglia was associated with alteration of a wide spectrum of CNS functions: perception, categorization, decision, and implicit learning, further emphasizing the central role of the basal ganglia as a substrate for synchronization of different neural activities.

According to the theory of the segregated parallel circuits, our findings would imply that all basal ganglia structures involved in the affected circuits were damaged. However, there is mounting evidence that these “parallel” circuits are interconnected both structurally and functionally (Joel 2001). This means that pathology of selected, strategically essential components have consequences in several functional domains. We consider that our findings are in consistence with this view of the basal ganglia functioning within a system of interconnected parallel circuits.

VI.

CONCLUSIONS

1. Damage of the striatum causes decreased cortical excitability, as shown by reduced amplitudes of the SEP and ERP amplitudes in HD and in focal lesions of the striatum.
2. The amplitude reduction of the median nerve SEPs in HD is proportional to the extent of the genetic mutation i.e. the length of the trinucleotide repeat.
3. Tibial nerve SEPs is a sensitive method to detect early pathophysiological changes in HD, being the only neurophysiological alteration in asymptomatic carriers of the mutation, in our studies.
4. Focal lesions of the striatum can differentially affect the cortical components of the median nerve SEPs, with more severe alteration of the frontal than the parietal components.
5. Perceptual categorization/decision process shows a specific pattern of alteration in HD, with consequence at the temporal recording sites, according to visual categorization-task ERPs. This was different from the ERP changes found in focal vascular lesions of the striatum and in PD.
6. Focal lesions of the striatum cause impairment in habit-learning (PCL).
7. Executive dysfunction (attentional set-shifting) can be independent of habit learning problems.

Taken together, these data suggest, that striatum plays a crucial role in the organisation of such distinct CNS functions as primary perception, perceptual categorisation/decision and habit learning. Thus clinical consequences of striatal damage must be thought off as a summation of these, multilevel malfunctions.

VII.

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VIII.

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